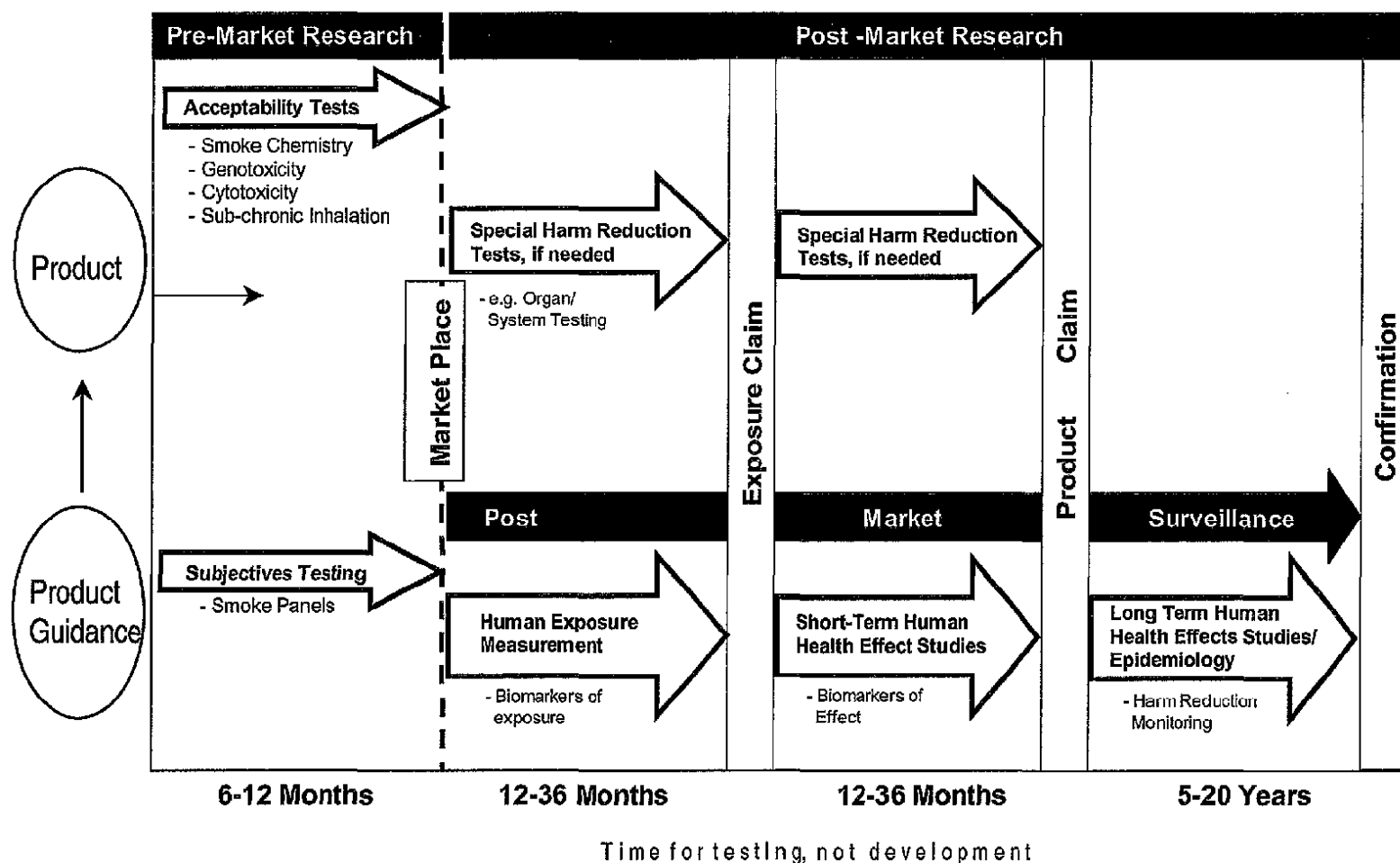


# Process for Reduced-Harm Product Use and Claims



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# Options Following Acceptability Testing

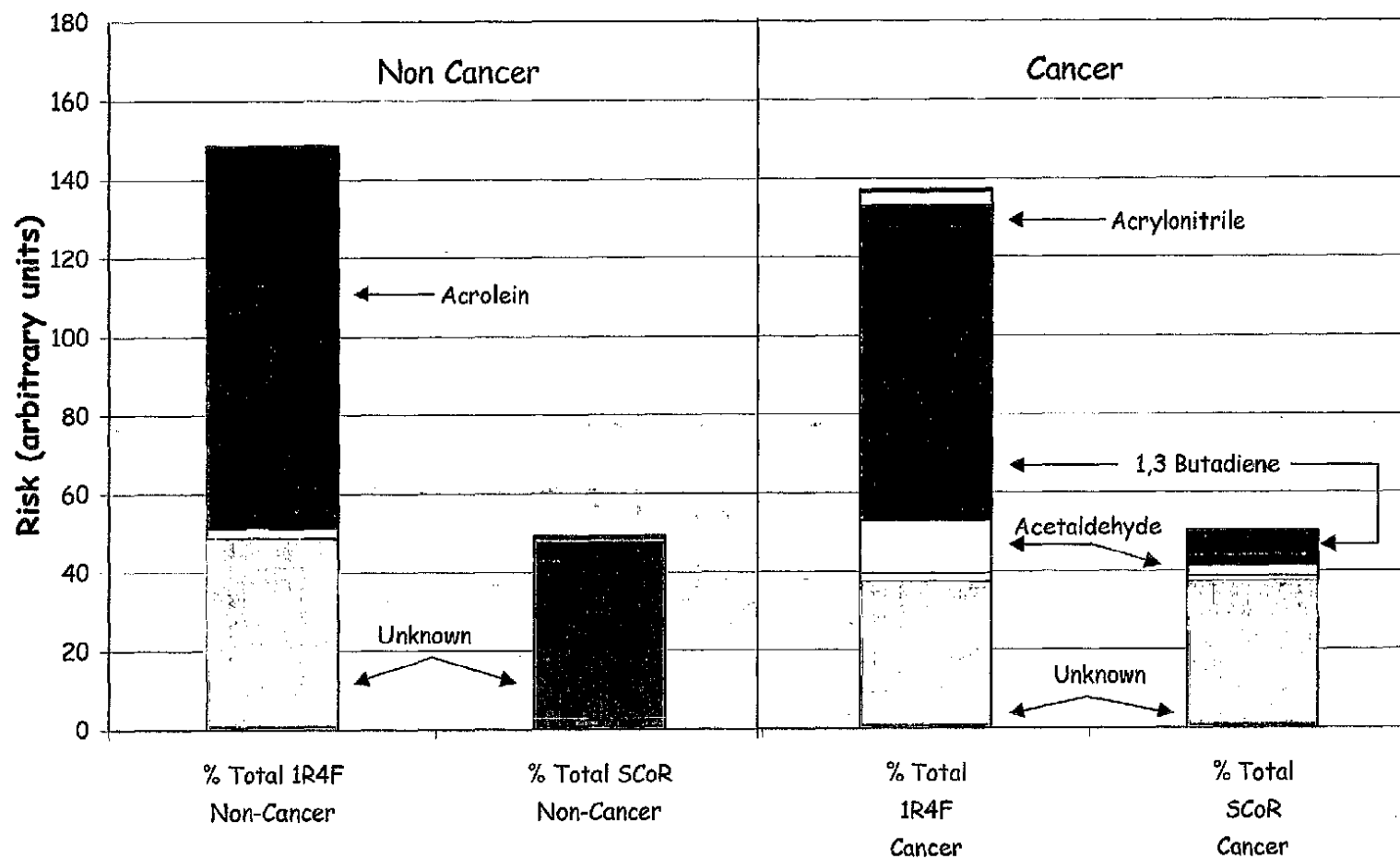
- Go to market without claims
- Conduct additional work (e.g. exposure in adult smokers over 21 years of age) in order to support claims

# IOM Principle 4

- “....that the product substantially reduces exposure to one or more tobacco toxicants ....”
- “ The ‘substantial reduction’ in exposure should be sufficiently large that independent scientific experts would anticipate finding a measurable reduction in morbidity and/or mortality in subsequent clinical or epidemiological studies.”

*(from IOM Principle 4)*

# Target Constituents



Unknown	Hydrogen cyanide	Formaldehyde	Acetaldehyde	Acrolein
Phenol	Vinyl chloride	1,3-Butadiene	Acrylonitrile	Benzene
Benz(a)anthracene	Benzo(-)fluoranthene	Benzo(a)pyrene	Indeno(1,2,3-cd)pyrene	NNN

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# Generic Clinical Development Plan for Reduced Harm Cigarettes

## 1. EXPOSURE TESTING

SMOKING  
TOPOGRAPHY STUDY

10 DAY SHORT TERM  
EXPOSURE STUDY

6-12 MONTHS LONG TERM  
EXPOSURE STUDY

time

# SCoR

## Study no 1: Smoking Topography

### Questions to be answered:

How do adult smokers smoke  
SCoR cigarettes?

**A single cigarette, 4-period  
crossover study with 16 adult  
smokers of light cigarettes**

# **SCoR**

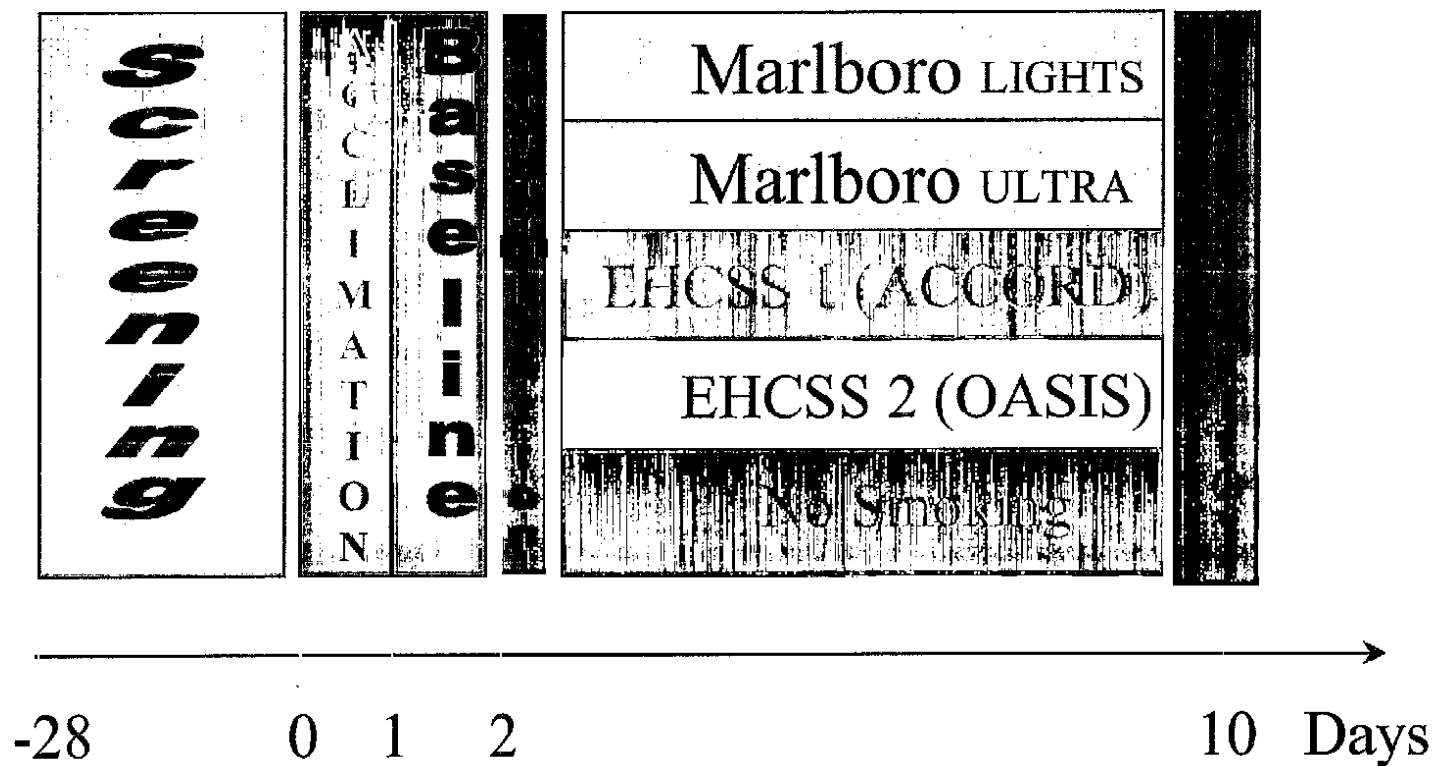
Study no 2: Short-Term Human Exposure

## **Questions to be answered:**

What is the exposure to selected  
smoke constituents to adult smokers  
of SCoR cigarettes?

**An 8 day controlled smoking study  
with 80 adult smokers of light  
cigarettes**

# Study Schedule EHCSS Study, 1169



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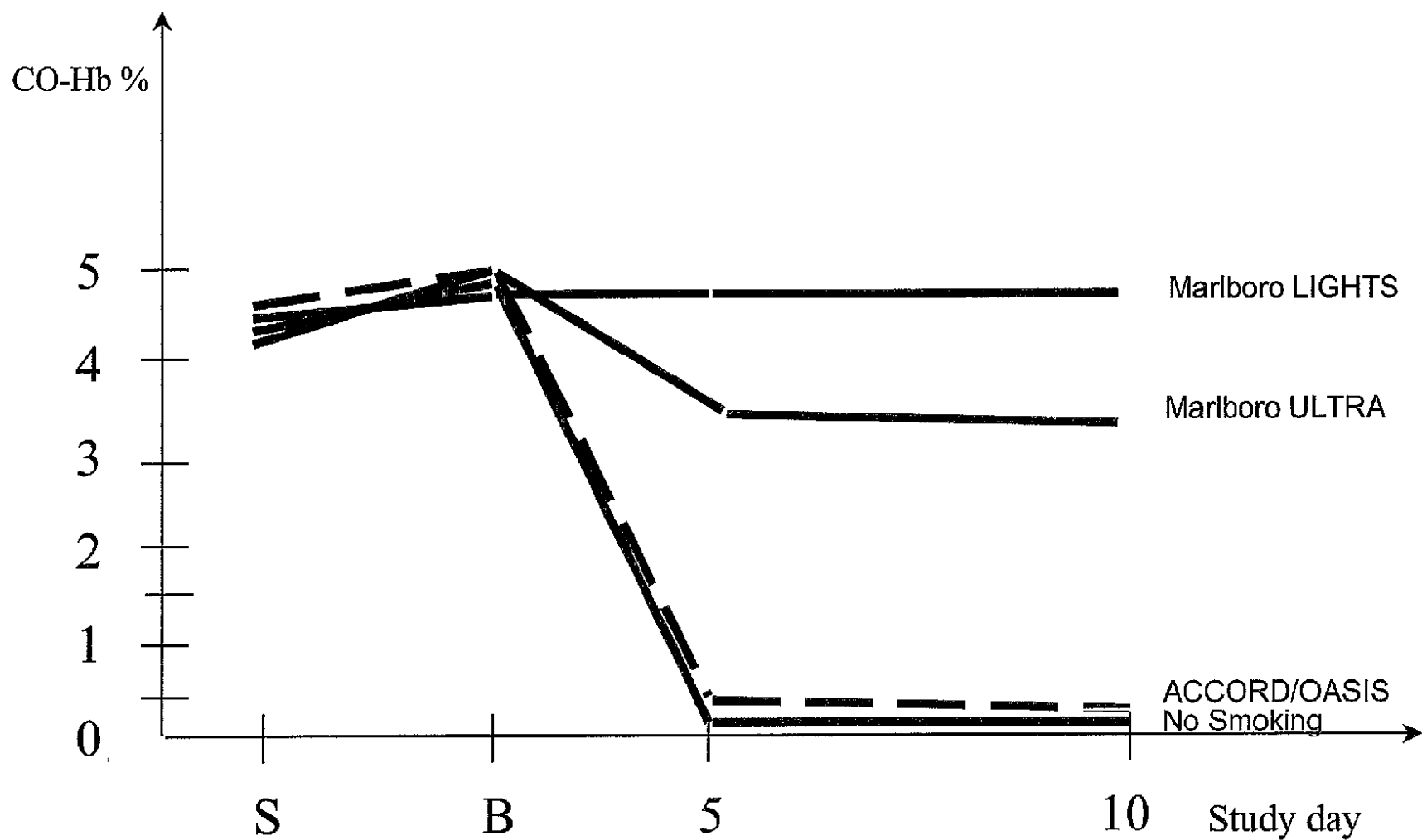


# Controlled Smoking

## Acclimation Day

- Subjects are allowed to smoke as many cigarettes as reported in their smoking history plus 20 % .
- Subjects are monitored for actual cigarette consumption to determine their daily allotment for the remainder of the study (day 2 - 10).
- This determines the *maximum daily allowance* (6 - 30 cigarettes per day).

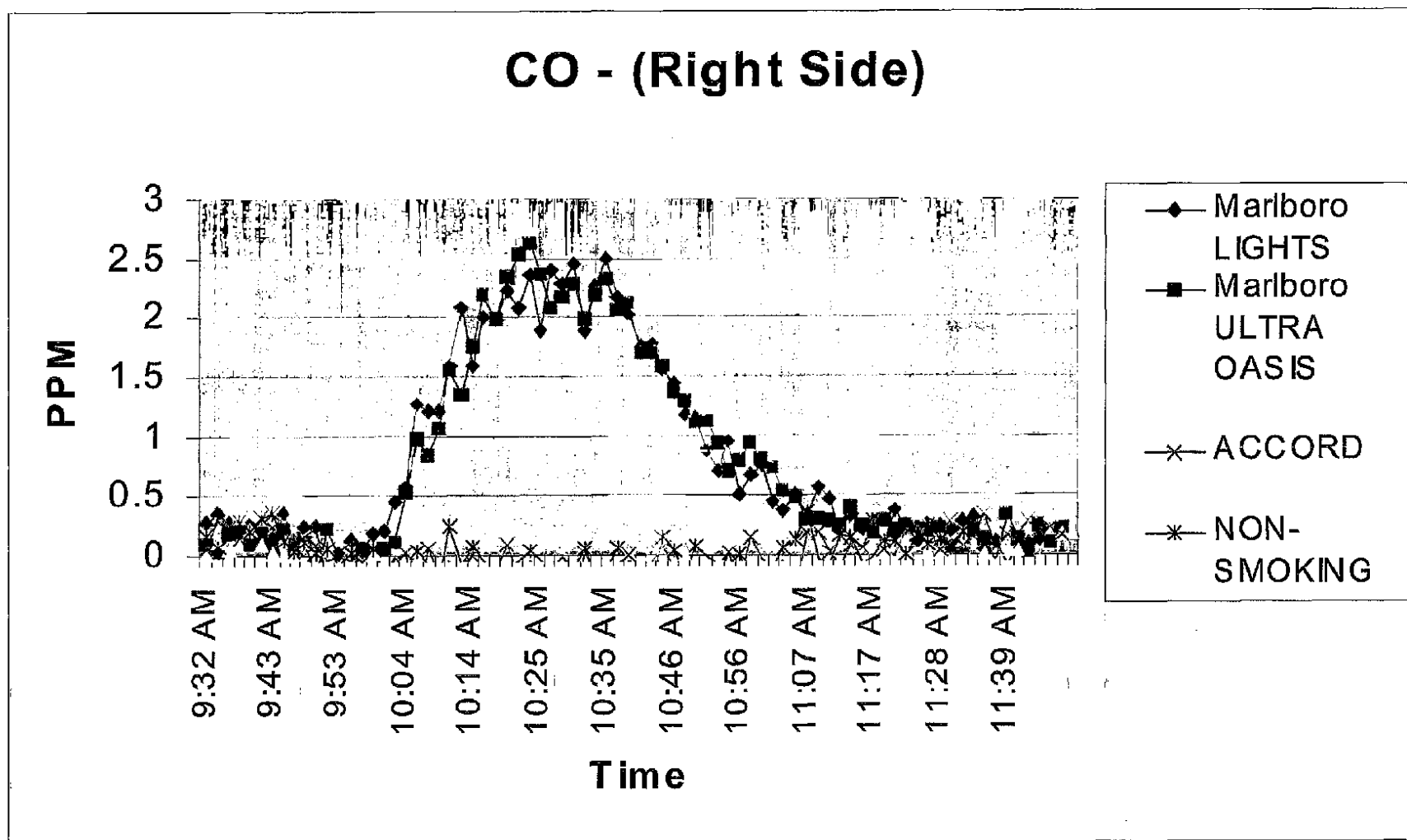
# Carboxy-hemoglobin in Blood



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10

# ETS Measurements



PM3001499032

# **SCoR**

## **Study no 2: Short-Term Human Exposure**

After baseline investigations adult smokers will be randomized to:

- A.** Continue to smoke light cigarettes (20)
- B.** Switch to SCoR cigarettes (40)
- C.** Switch to a reference brand (20)

# SCoR

## Study no 3: Long-Term Human Exposure

Questions to be answered:

What is the exposure to selected smoke constituents to adult smokers of SCoR cigarettes during non-restricted smoking?

**A non-restricted smoking, ambulatory,  
6-months study with 200 adult  
smokers of light cigarettes**

# **SCoR**

## **Study no 3: Long-Term Human Exposure**

**After baseline investigations adult smokers will be randomized to:**

- A. Continue to smoke light cigarettes**
- B. Switch to SCoR cigarettes**
- C. Switch to a reference brand**

# **SCoR**

## **Clinical Development Plan**

- **Study no 1: Smoking Topography**  
**November 01 - April 03**
- **Study no 2: Short Term Human Exposure**  
**November 01 - February 03**
- **Study no 3: Long term Human Exposure and Biomarkers of Potential Harm**  
**November 01 - October 03**

# **SCoR**

## Potential Issues

- The clinical development plan is based on several assumptions since experience in this research area is entirely lacking
- Results from our first pilot studies are not yet available and may change the plan



# SCoR

## Potential Issues

- Method development and validation of bioanalytical assays is an essential prerequisite for both exposure studies
- Are we measuring enough biomarkers of exposure?